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(54) **METHOD FOR PREPARING S-NICOTINE**

VERFAHREN ZUR HERSTELLUNG VON S-NIKOTIN

PROCÉDÉ DE PRÉPARATION DE S-NICOTINE

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EP 4 140 992 B1

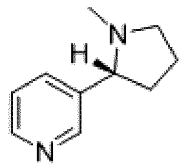
Description

TECHNICAL FIELD

[0001] The present invention relates to the technical field of chemical synthesis, and particularly relates to a preparation method of S-nicotine.

BACKGROUND ART

[0002] With the rapid development of e-cigarette industry, the demand of nicotine, which is one of the important active ingredients of e-cigarette, is increasing, among which nicotine in a single configuration with optical activity is widely concerned. S-Nicotine has a molecular formula of $C_{10}H_{14}N_2$, a CAS number of 54-11-5, and a structural formula of



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[0003] At present, there are few studies on the preparation methods of S-nicotine. S-nicotine is basically obtained by a chiral resolution method, but chiral resolution reagents are expensive, which is not conducive to industrial production.

[0004] A patent with a publication No. CN104341390A discloses a preparation method of S-nicotine. According to the method, cyclic imine is used as a starting material, an expensive chiral catalyst is required, high-pressure hydrogen equipment is required, and the production cost is relatively high, so that the method is not suitable for large-scale industrial production. A patent with a publication No. CN11233829A discloses a preparation method of nicotine with optical activity. According to the method, a chiral ligand containing nitrogen or phosphorus is used to prepare an organometallic catalyst, an imide derivative is used as a stating material to prepare S-nicotine, the preparation of the organometallic catalyst is relatively complicated, the production cost is relatively high, and the yield of S-nicotine is relatively low.

[0005] In the prior art, there are known some methods or devices as described in their respective documents. An article with a title of "A New and Efficient Approach to the Synthesis of Nicotine and Anabasine Analogues" discloses that a straightforward and practical approach was established for the synthesis of nicotine and anabasine analogues by the cyclization of mesylated 1-(3-pyridinyl)-1,4, and 1,5-diol derivatives to form the pyrrolidino or piperidino fragments. Nicotine analogue (S)-15 was prepared with good enantioselectivity using the developed azacyclization procedure of nonracemic (R)-1-pyridin-3-ylbutane-1.4-diol, which was obtained by the borane-mediated reduction of ketone 12 in the presence of the spiroborate ester derived from diphenyl prolinol and ethylene glycol. The patent application EP 3925955 A1 discloses a method for preparing nicotine. The nicotinic acid alkyl ester and N-methylpyrrolidone are subjected to a condensation reaction, and then added with a strong acid to obtain 4-methyamino-1-(3-pyridine)-butanonehydrochloride. The 4-methylamino-1-(3-pyridine)-butanone hydrochloride is reacted with an amino-protecting reagent to obtain an intermediate. A chiral alcohol is obtained through an asymmetric reduction. The chiral alcohol is converted into the nicotine through a two-step reaction. The patent application CN 104341390 A discloses asymmetric synthesis method of plant-based pesticides nicotine and quinine, in which hydrogenation precursor cyclic imine is obtained by using inexpensive and readily available 2,5-dibromopyridine as the starting material through two-step reactions, important hydrogenation product intermediates are obtained with high enantioselectivity under the induction of chiral catalyst iridium phosphine oxazoline, and the intermediates are reacted after two steps to obtain L-nicotine, while the intermediates can be converted to L-quinine after one step reaction.

[0006] Therefore, the present application provides a preparation method of S-nicotine, cheaper and readily available raw materials are used, and the yield of prepared S-nicotine is higher.

SUMMARY

[0007] In order to increase the yield of S-nicotine, the present application provides a preparation method of S-nicotine.

[0008] In a first aspect, the present application provides a preparation method of S-nicotine, which is implemented by adopting the following technical solutions:

a preparation method of S-nicotine, including the following steps:

S1: adding nicotinate and γ-butyrolactone into an organic solvent I, performing condensation in the presence of a base catalyst to obtain a condensation product, and performing cyclization on the condensation product in the

presence of hydrochloric acid to obtain 4-chloro-1-(3-pyridin)-1-butanone;
S2: reacting the 4-chloro-1-(3-pyridin)-1-butanone with an amination reagent under alkaline conditions to obtain 4-amino-1-(3-pyridin)-1-butanone;
S3: adding the 4-amino-1-(3-pyridin)-1-butanone and (+)-B-diisopinocampheyl chloroborane into an organic solvent II, and reacting at -30 to 10°C to obtain (S)-4-amino-1-(pyridin-3-yl)butan-1-ol;
S4: reacting the (S)-4-amino-1-(pyridin-3-yl)butan-1-ol with a chlorination reagent to obtain (S)-4-amino-1-(pyridin-3-yl)butyl-1-chlorine;
S5: performing cyclization on the (S)-4-amino-1-(pyridin-3-yl)butyl-1-chlorine in the presence of a base to obtain S-demethylnicotine; and
S6: reacting the S-demethylnicotine with an amine methylation reagent to obtain crude S-nicotine, and purifying to obtain S-nicotine.

[0009] By adopting the above technical solution, nicotinate and γ-butyrolactone are used as raw materials, nicotinate and γ-butyrolactone are both cheap and readily available raw materials, (+)-B-diisopinocampheyl chloroborane is used to reduce a carbonyl group of an intermediate and obtain a target chiral center; the (+)-B-diisopinocampheyl chloroborane induces the production of a chiral hydroxyl group, chlorination and cyclization are performed to form chiral S-demethyl-nicotine, and finally amine methylation is performed to obtain S-nicotine with photochemical activity. The preparation method of S-nicotine provided in the present application has the advantages of high purity, simple process, easy operation, high yield and mild reaction conditions, and S-nicotine in a single configuration is obtained with a high ee value, which is suitable for industrial production.

[0010] In the present application, the nicotinate is methyl nicotinate or ethyl nicotinate.

[0011] Preferably, at S1, a molar ratio of the nicotinate to the γ-butyrolactone to the base catalyst is 1: (1-2): (1.2-3); and more preferably, the molar ratio of the nicotinate to the γ-butyrolactone to the base catalyst is 1: 1:2.

[0012] In the present application, the alkali metal alkoxide includes, but is not limited to, any one of sodium tert-butoxide, sodium methoxide, sodium ethoxide, and potassium tert-butoxide.

[0013] In the present application, the alkaline earth metal hydride includes, but is not limited to, one or more of NaH, LiH, and KH.

[0014] In the present application, the alkaline earth metal oxide includes, but is not limited to, one or more of Na_2O, Li_2O, and K_2O.

[0015] In the present application, the amine includes, but is not limited to, triethylamine and/or diisopropylethyl amine.

[0016] In the present application, the metal salt of amine includes, but is not limited to, sodium bis(trimethylsilyl)amide and/or lithium diisopropylamide.

[0017] In the present application, the hydroxide includes, but is not limited to, one or more of sodium hydroxide, lithium hydroxide, and magnesium hydroxide.

[0018] In the present application, the carbonate includes, but is not limited to, one or more of sodium carbonate, potassium carbonate, and cesium carbonate.

[0019] In the present application, the bicarbonate includes, but is not limited to, sodium bicarbonate and/or potassium bicarbonate.

[0020] More preferably, the base catalyst is selected from any one of sodium tert-butoxide, NaH, and potassium tert-butoxide.

[0021] In the present application, at S1, the organic solvent I is selected from one or more of tetrahydrofuran, methyl tertiary butyl ether, dimethyl tetrahydrofuran, and 1,4-dioxane; and preferably, the organic solvent I is 1,4-dioxane.

[0022] In the present application, at S1, the reaction needs to be performed under an N_2 atmosphere, and an adding order of the nicotinate, the γ-butyrolactone and the base catalyst is that: the γ-butyrolactone is added first, followed by the base catalyst and finally the nicotinate.

[0023] In the present application, the reaction temperature of the γ -butyrolactone and the base catalyst is 0°C, and the reaction time is 30 min; and the reaction temperature of the nicotinate, the γ -butyrolactone and the base catalyst is 25°C.

[0024] In the present application, at S1, the hydrochloric acid is concentrated hydrochloric acid, and the concentration of the concentrated hydrochloric acid is 12 mol/L.

[0025] In the present application, at S1, a molar ratio of the condensation product to HCl in the hydrochloric acid is 1: (1-6); and preferably, the molar ratio of the condensation product to the HCl in the hydrochloric acid is 1: 1.

[0026] In the present application, at S1, the reflux reaction time of the condensation product and the hydrochloric acid at 70 to 90°C is 0.5 to 1.5 h; and preferably, the reflux reaction time of the condensation product and the hydrochloric acid at 80°C is 1 h.

[0027] In the present application, at S1, after cyclization is performed on the condensation product in the presence of hydrochloric acid, post-processing is further required to obtain the 4-chloro-1-(3-pyridin)-1-butanone, wherein the post-processing includes: diluting with saline, neutralizing with a base substance, extracting, taking an organic phase, and

performing rotary drying for removing the solvent to obtain the 4-chloro-1-(3-pyridin)-1-butanone.

[0028] In the present application, before the reaction of S2, the 4-chloro-1-(3-pyridin)-1-butanone obtained at S1 needs to be dissolved in a solvent. The solvent includes, but is not limited to, one or more of acetonitrile, 1,4-dioxane, dichloromethane, DMF, and tetrahydrofuran; and preferably, the solvent is acetonitrile.

[0029] In the present application, at S2, the reaction temperature of the 4-chloro-1-(3-pyridin)-1-butanone and the animation reagent under the alkaline conditions is 60 to 100°C, and the reaction time is 6 to 10 h; and preferably, the reaction temperature of the 4-chloro-1-(3-pyridin)-1-butanone and the animation reagent under the alkaline conditions is 80°C, and the reaction time is 8 h.

[0030] Preferably, at S2, the molar ratio of the 4-chloro-1-(3-pyridin)-1-butanone to the animation reagent is 1: 2.

[0031] Preferably, at S2, the amination reagent is ammonium hydroxide or formamide; and more preferably, the amination reagent is formamide.

[0032] In the present application, at S2, the pH of an alkaline environment in the reaction of the 4-chloro-1-(3-pyridin)-1-butanone and the amination reagent under the alkaline conditions is 8 to 12; and preferably, the pH of the alkaline environment in the reaction of the 4-chloro-1-(3-pyridin)-1-butanone and the amination reagent under the alkaline conditions is 9. The alkaline environment can be adjusted with a 52 wt% NaOH aqueous solution.

[0033] In the present application, S2 further includes a post-processing step, wherein the post-processing step includes: adjusting the pH to 6 to 7 by adding an acid, extracting, performing rotary drying on an organic phase for removing the solvent to obtain the 4-amino-1-(3-pyridin)-1-butanone.

[0034] In the present application, at S3, the 4-amino-1-(3-pyridin)-1-butanone prepared at S2 needs to be dissolved in the organic solvent II.

[0035] Preferably, at S3, the organic solvent II is tetrahydrofuran.

[0036] Preferably, at S3, a molar ratio of the 4-amino-1-(3-pyridin)-1-butanone to the (+)-B-diisopinocampheyl chloroborane is 1: (1-3); and more preferably, the molar ratio of the 4-amino-1-(3-pyridin)-1-butanone to the (+)-B-diisopinocampheyl chloroborane is 1: (1.5-2).

[0037] Preferably, at S3, the reaction temperature of the 4-amino-1-(3-pyridin)-1-butanone and the (+)-B-diisopinocampheyl chloroborane is 0°C, and the reaction time is 2 h.

[0038] In the present application, S3 further includes an extraction step, wherein an extraction agent is methylene chloride, after the extraction, rotary drying for removing the solvent is performed to obtain the (S)-4-amino-1-(pyridin-3-yl)butan-1-ol.

[0039] In the present application, at S4, the (S)-4-amino-1-(pyridin-3-yl)butan-1-ol prepared at S3 needs to be dissolved in a solvent and then react with the chlorination reagent. The solvent includes, but is not limited to, 1,4-dioxane.

[0040] Preferably, the reaction temperature of S4 is -10 to 10°C; and more preferably, the reaction temperature of S4 is 0°C.

[0041] In the present application, the reaction time of S4 is 20 to 40 min; and preferably, the reaction time of S4 is 30 min.

[0042] Preferably, at S4, the chlorination reagent is selected from oxalyl chloride, thionyl chloride, PC13, and PC15.

[0043] Preferably, at S4, the molar ratio of the (S)-4-amino-1-(pyridin-3-yl)butan-1-ol to the oxalyl chloride is 1: 1.5.

[0044] In the present application, at S4, after the (S)-4-amino-1-(pyridin-3-yl)butan-1-ol reacts with the oxalyl chloride, quenching is required to obtain a mixture containing (S)-4-amino-1-(pyridin-3-yl)butyl-1-chlorine, wherein a quenching reagent may be water.

[0045] In the present application, at S5, cyclization is performed on the mixture containing (S)-4-amino-1-(pyridin-3-yl)butyl-1-chlorine prepared at S4 in the presence of a base to form the S-demethylnicotine.

[0046] Preferably, at S5, the base is hydroxide or carbonate.

[0047] In the present application, the hydroxide includes, but is not limited to, one or more of sodium hydroxide, potassium hydroxide, lithium hydroxide, cesium hydroxide, barium hydroxide, and magnesium hydroxide.

[0048] In the present application, the carbonate includes, but is not limited to, one or more of sodium carbonate, potassium carbonate, and cesium carbonate.

[0049] More preferably, the base is sodium hydroxide.

[0050] In the present application, at S5, a molar ratio of the (S)-4-amino-1-(pyridin-3-yl)butyl-1-chlorine and the sodium hydroxide is 1: (1.5-2.5); and preferably, the molar ratio of the (S)-4-amino-1-(pyridin-3-yl)butyl-1-chlorine and the sodium hydroxide is 1:2.

[0051] In the present application, at S5, the reaction temperature of the mixture containing (S)-4-amino-1-(pyridin-3-yl)butyl-1-chlorine prepared at S4 and the base is 55 to 65°C, and the reaction time is 2 to 3 h; and preferably, the reaction temperature of the mixture containing (S)-4-amino-1-(pyridin-3-yl)butyl-1-chlorine prepared at S4 and the base is 60°C, and the reaction time is 2 h.

[0052] In the present application, a mixture containing S-demethylnicotine is obtained at S5.

[0053] In the present application, at S6, the amine methylation reagent is methyl iodide.

[0054] In the present application, at S6, a molar ratio of S-demethylnicotine in the mixture containing S-demethylnicotine to the methyl iodide is 1: (1.1-1.4); and preferably, the molar ratio of the S-demethylnicotine in the mixture containing

S-demethylnicotine to the methyl iodide is 1: 1.2.

[0055] In the present application, at S6, the reaction temperature of the mixture containing S-demethylnicotine and the amine methylation reagent is 20 to 30°C, and the reaction time is 2 to 4 h; and preferably, the reaction temperature of the mixture containing S-demethylnicotine and the amine methylation reagent is 25°C, and the reaction time is 3 h.

[0056] In the present application, at S6, after the mixture containing S-demethylnicotine reacts with the amine methylation reagent, the pH needs to be adjusted to 6 by using an acid, extraction is performed, an organic phase is dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude S-nicotine.

[0057] In the present application, at S6, the purification is distillation purification, and specifically includes: performing atmospheric distillation extraction two times to obtain a levorotatory sample with high purity.

[0058] In summary, the present application has the following beneficial effects:

[0059] The present application provides a novel route for synthesizing S-nicotine by using cheap and readily available nicotinate and γ-butyrolactone as starting materials, and the cost is low. Condensation is performed in the presence of a base catalyst, cyclization is performed through a reflux reaction with concentrated hydrochloric acid to obtain 4-chloro-1-(3-pyridin)-1-butanone, a reaction is performed with an amination reagent under alkaline conditions to obtain 4-amino-1-(3-pyridin)-1-butanone, the production of a chiral hydroxyl group is induced by (+)-B-diisopinocampheyl chloroborane to obtain (S)-4-amino-1-(pyridin-3-yl)butan-1-ol, chlorination and cyclization in the presence of a base are performed to obtain S-demethylnicotine, and finally amine methylation is performed to obtain S-nicotine. The reaction route is simple, the reaction conditions are mild and easy to operate, S-nicotine in a single configuration is obtained with high selectivity, the yield and the purity of S-nicotine are high, and the steps are simple, so that the method is particularly suitable for industrial production of S-nicotine.

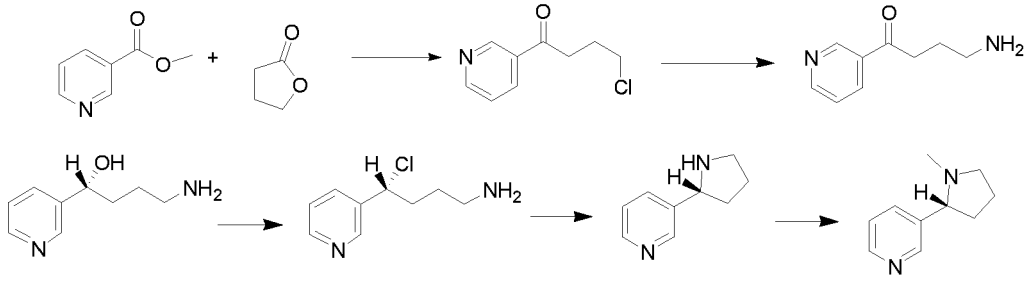
DETAILED DESCRIPTION

[0060] The present application will be described in detail below in conjunction with embodiments.

[0061] The raw materials used in the present application can be obtained commercially, and if there is no special description, the raw materials not mentioned in the present application are purchased from Sinopharm Chemical Reagent Co., Ltd.

[0062] Embodiments 1 to 20 provide a preparation method of S-nicotine, which will be described below by taking Embodiment 1 as an example.

[0063] Embodiment 1 provides a preparation method of S-nicotine, wherein nicotinate is methyl nicotinate, and a synthetic route is shown as Reaction Formula 1:



Reaction Formula 1

[0064] Specific preparation steps were as follows:

S1: 86.1 g (1 mol, 1 eq) of γ-butyrolactone (with a CAS No. of 96-48-0) was added into 1 L of 1,4-dioxane at 0°C and mixed, 48 g (2 mol, 2 eq) of sodium hydride was added, a reaction was performed at 0°C for 0.5 h, 137.1 g (1 mol) of methyl nicotinate (with a CAS No. of 93-60-7) was added, a condensation reaction was performed at 25°C and monitored by TLC until the end of the reaction to obtain a condensation product, 0.083 L of 12 mol/L (1 mol, 1 eq) hydrochloric acid was added into the condensation product, a reflux reaction was performed at 80°C for 1 h, a saturated salt solution was added for extraction, sodium bicarbonate was added to adjust the pH of the system to 7, extraction was performed three times by using dichloromethane, and organic phases were combined and subjected to rotary drying for removing the solvent to obtain 4-chloro-1-(pyridin-3-yl)-1-butanone.

S2: the 4-chloro-1-(pyridin-3-yl)-1-butanone obtained at S1 was dissolved in 1 L of acetonitrile, a 52 wt% NaOH aqueous solution was used to adjust pH of the system to 9, 90.1 g (2 mol, 2 eq) of formamide was added, a reaction

was performed at 80°C for 8 h, after the reaction, 4 mol/L hydrochloric acid was used to adjust the pH to 6, extraction was performed by using ethyl acetate, an organic phase was taken and subjected to rotary evaporation for removing the solvent to obtain 4-amino-1-(pyridin-3-yl)-1-butanone.

S3: the 4-amino-1-(pyridin-3-yl)-1-butanone obtained at S2 was dissolved in 5 L of tetrahydrofuran, after the dissolution, 641.5 g (2 mol, 2 eq) of (+)-B-diisopinocampheyl chloroborane was added at 0°C, a reaction was performed at 0°C for 2 h, extraction was performed three times by using dichloromethane, and rotary drying for removing the solvent was performed to obtain (S)-4-amino-1-(pyridin-3-yl)butan-1-ol.

S4: 2 L of 1,4-dioxane was added into the (S)-4-amino-1-(pyridin-3-yl)butan-1-ol obtained at S3 and mixed, 190.4 g (1.5 mol, 1.5 eq) of oxalyl chloride was added at 0°C, a reaction was performed at 0°C for 30 min, and quenching was performed by adding 10 mL of water to obtain a mixture containing (S)-4-amino-1-(pyridin-3-yl)butyl-1-chlorine.

S5: 80 g (2 mol, 2 eq) of NaOH was added into the mixture containing (S)-4-amino-1-(pyridin-3-yl)butyl-1-chlorine prepared at S4 and dissolved under stirring, and at the same time, a reaction was performed at 60°C for 2 h to obtain a mixture containing S-demethylnicotine; and

S6: 170.3 g (1.2 mol, 1.2 eq) of methyl iodide was added into the mixture containing S-demethylnicotine prepared at S5, a reaction was performed at 25°C for 3 h, the pH of the system was adjusted to 6 by using 12 mol/L hydrochloric acid, extraction was performed by using dichloromethane, an organic phase was taken, dried over Na_2SO_4, and concentrated under reduced pressure for removing the solvent to obtain crude S-nicotine, and the crude S-nicotine was further purified once by atmospheric distillation to obtain S-nicotine with a yield of 52%, an ee value of 98%, and a purity o 99%.

[0065] It is worthwhile to note that each mass and specific molar weight in the embodiments of the present application can be selected according to the size of an industrially produced vessel as long as the equivalence ratio of each reaction raw material is consistent.

[0066] A difference between Embodiments 2 to 3 and Embodiment 1 is that: in the reaction of S1, the kind of the base catalyst was adjusted as specifically shown in Table 1.

Table 1 Effect of selection of base catalyst on the yield of S-nicotine

Serial number	Selection of base catalyst	Yield of S-nicotine (%)
Embodiment 1	Sodium hydride	52
Embodiment 2	Sodium tert-butoxide	42
Embodiment 3	Potassium tert-butoxide	43

[0067] A difference between Embodiment 4 and Embodiment 1 is that: in the reaction of S2, the kind of the amination reagent was adjusted as specifically shown in Table 2.

Table 2 Effect of selection of amination reagent on the yield of S-nicotine

Serial number	Selection of amination reagent	Yield of S-nicotine (%)
Embodiment 1	Formamide	52
Embodiment 4	Ammonium hydroxide	48

[0068] A difference between Embodiments 5 to 6 and Embodiment 1 is that: in the reaction of S2, the usage amount of the amination reagent was adjusted as specifically shown in Table 3.

Table 3 Effect of usage amount of amination reagent on the yield of S-nicotine

Serial number	Equivalent quantity (eq) of amination reagent	Yield of S-nicotine (%)
Embodiment 1	2	52
Embodiment 5	3	48
Embodiment 6	1	45

[0069] A difference between Embodiments 7 to 9 and Embodiment 1 is that: in the reaction of S3, the usage amount of the (+)-B-diisopinocampheyl chloroborane was adjusted as specifically shown in Table 4.

Table 4 Effect of usage amount of (+)-B-diisopinocampheyl chloroborane on the yield of S-nicotine

Serial number	Equivalent quantity (eq) of (+)-B-diisopinocampheyl chloroborane	Yield of S-nicotine (%)
Embodiment 1	2	52
Embodiment 7	1	42
Embodiment 8	3	46
Embodiment 9	1.5	48

[0070] A difference between Embodiments 10 to 12 and Embodiment 1 is that: in the reaction of S3, the kind of the organic solvent II was adjusted as specifically shown in Table 5. Examples 11 and 12 are only comparative examples which are not examples according to the invention.

Table 5 Effect of selection of organic solvent II on the yield of S-nicotine

Serial number	Selection of organic solvent II	Yield of S-nicotine (%)
Embodiment 1	Tetrahydrofuran	52
Embodiment 10	1,4-dioxane	50
Embodiment 11	Methyl tertiary butyl ether	25
Embodiment 12	Absolute ether	48

[0071] A difference between Embodiments 13 to 15 and Embodiment 1 is that: in the reaction of S3, the reaction temperature was adjusted as specifically shown in Table 6.

Table 6 Effect of reaction temperature on the yield of S-nicotine

Serial number	Reaction temperature (°C)	Yield of S-nicotine (%)
Embodiment 1	0	52
Embodiment 13	-30	50
Embodiment 14	10	45
Embodiment 15	5	48

[0072] A difference between Embodiments 16 to 17 and Embodiment 1 is that: in the reaction of S4, the reaction temperature was adjusted as specifically shown in Table 7.

Table 7 Effect of reaction temperature on the yield of S-nicotine

Serial number	Reaction temperature (°C)	Yield of S-nicotine (%)
Embodiment 1	0	52
Embodiment 16	10	43
Embodiment 17	-10	48

[0073] A difference between Embodiments 18 to 19 and Embodiment 1 is that: in the reaction of S4, the usage amount of the oxalyl chloride was adjusted as specifically shown in Table 8.

Table 8 Effect of usage amount of oxalyl chloride on the yield of S-nicotine

Serial number	Equivalent quantity (eq) of oxalyl chloride	Yield of S-nicotine (%)
Embodiment 1	1.5	52
Embodiment 18	1	48

(continued)

Serial number	Equivalent quantity (eq) of oxalyl chloride	Yield of S-nicotine (%)
Embodiment 19	2	35

[0074] A difference between Embodiment 20 and Embodiment 1 is that: at S1, the methyl nicotinate was replaced with equimolar ethyl nicotinate (with a CAS No. of 614-18-6), and produced S-nicotine had a yield of 52%, an ee value of 98%, and a purity of 99%.

[0075] The specific embodiments are merely an explanation of the present application and are not intended to limit the present application. After reading the present description, those skilled in the art can make modifications to the present embodiments as required without any inventive contribution, and these modifications shall fall within the scope of protection of the present application.

Claims

1. A preparation method of S-nicotine, **characterized by** comprising the following steps:

   S1: adding nicotinate and γ-butyrolactone into an organic solvent I, performing condensation in the presence of a base catalyst to obtain a condensation product, and performing cyclization on the condensation product in the presence of hydrochloric acid to obtain 4-chloro-1-(3-pyridin)-1-butanone;
   S2: reacting the 4-chloro-1-(3-pyridin)-1-butanone with an amination reagent under alkaline conditions to obtain 4-amino-1-(3-pyridin)-1-butanone;
   S3: adding the 4-amino-1-(3-pyridin)-1-butanone and (+)-B-diisopinocampheyl chloroborane into an organic solvent II, and reacting at -30 to 10°C to obtain (S)-4-amino-1-(pyridin-3-yl)butan-1-ol;
   S4: reacting the (S)-4-amino-1-(pyridin-3-yl)butan-1-ol with a chlorination reagent to obtain (S)-4-amino-1-(pyridin-3-yl)butyl-1-chlorine;
   S5: performing cyclization on the (S)-4-amino-1-(pyridin-3-yl)butyl-1-chlorine in the presence of a base to obtain S-demethylnicotine; and
   S6: reacting the S-demethylnicotine with an amine methylation reagent to obtain crude S-nicotine, and purifying to obtain S-nicotine;
   wherein at S1, the base catalyst is selected from one or more of alkali metal alkoxide, alkaline earth metal hydride, alkaline earth metal oxide, amine, a metal salt of amine, hydroxide, carbonate, and bicarbonate;
   at S3, the organic solvent II is selected from one or more of tetrahydrofuran, dimethyl tetrahydrofuran, and 1,4-dioxane;
   at S4, the chlorination reagent is oxalyl chloride; and a molar ratio of the (S)-4-amino-1-(pyridin-3-yl)butan-1-ol to the oxaloyl chloride is 1: (1-3); and
   at S2, a molar ratio of the 4-chloro-1-(3-pyridin)-1-butanone to the amination reagent is 1: (1-3).

2. The preparation method of S-nicotine according to claim 1, **characterized in that** at S3, a molar ratio of the 4-amino-1-(3-pyridin)-1-butanone to the (+)-B-diisopinocampheyl chloroborane is 1: (1-3).

3. The preparation method of S-nicotine according to claim 4, **characterized in that** at S4, the reaction temperature is -10 to 10°C.

4. The preparation method of S-nicotine according to claim 1, **characterized in that** at S2, the amination reagent is ammonium hydroxide or formamide.

5. The preparation method of S-nicotine according to claim 1, **characterized in that** at S1, a molar ratio of the nicotinate to the γ-butyrolactone to the base catalyst is 1: (1-2): (1.2-3).

6. The preparation method of S-nicotine according to claim 1, **characterized in that** at S5, the base is hydroxide or carbonate.

Patentansprüche

1. Verfahren zur Herstellung von S-Nicotin, **dadurch gekennzeichnet, dass** es die folgenden Schritte umfasst:

S1: Zugabe von Nikotinat und γ-Butyrolacton in ein organisches Lösungsmittel I, Durchführung einer Kondensation in Gegenwart eines basischen Katalysators, um ein Kondensationsprodukt zu erhalten, und Durchführung einer Cyclisierung des Kondensationsprodukts in Gegenwart von Salzsäure, um 4-Chlor-1-(3-pyridin)-1-butanon zu erhalten;
S2: Umsetzen des 4-Chlor-1-(3-pyridin)-1-butanons mit einem Aminierungsreagenz unter alkalischen Bedingungen, um 4-Amino-1-(3-pyridin)-1-butanon zu erhalten;
S3: Zugabe von 4-Amino-1-(3-pyridin)-1-butanon und (+)-B-Diisopinocampheylchlorboran in ein organisches Lösungsmittel II und Umsetzen bei -30 bis 10°C um (S)-4-Amino-1-(pyridin-3-yl)butan-1-ol zu erhalten;
S4: Umsetzen des (S)-4-Amino-1-(pyridin-3-yl)butan-1-ols mit einem Chlorierungsreagenz, um (S)-4-Amino-1-(pyridin-3-yl)butyl-1-chlor zu erhalten;
S5: Cyclisierung des (S)-4-Amino-1-(pyridin-3-yl)butyl-1-chlorins in Gegenwart einer Base, um S-Demethylnicotin zu erhalten; und
S6: Umsetzen des S-Demethylnicotins mit einem Amin-Methylierungsreagenz, um rohes S-Nicotin zu erhalten, und Reinigen, um S-Nicotin zu erhalten;
wobei bei S1 der Basenkatalysator aus einem oder mehreren von Alkalimetallalkoxid, Erdalkalimetallhydrid, Erdalkalimetalloxid, Amin, einem Metallsalz von Amin, Hydroxid, Carbonat und Bicarbonat ausgewählt ist;
bei S3 das organische Lösungsmittel II ausgewählt ist aus einem oder mehreren von Tetrahydrofuran, Dimethyltetrahydrofuran und 1,4-Dioxan,
bei S4 das Chlorierungsreagenz Oxalylchlorid ist, und ein molares Verhältnis des (S)-4-Amino-1-(pyridin-3-yl)butan-1-ols zum Oxalylchlorid 1:(1-3) ist, und
bei S2 ein molares Verhältnis des 4-Chlor-1-(3-pyridin)-1-butanons zum Aminierungsreagenz 1:(1-3) ist.

2. Verfahren zur Herstellung von S-Nicotin nach Anspruch 1, **dadurch gekennzeichnet, dass** bei S3 ein molares Verhältnis des 4-Amino-1-(3-pyridin)-1-butanons zum (+)-B-Diisopinocampheylchlorboran 1:(1-3) ist.

3. Verfahren zur Herstellung von S-Nicotin nach Anspruch 4, **dadurch gekennzeichnet, dass** bei S4 die Reaktionstemperatur -10 bis 10°C beträgt.

4. Verfahren zur Herstellung von S-Nikotin nach Anspruch 1, **dadurch gekennzeichnet, dass** bei S2 das Aminierungsreagenz Ammoniumhydroxid oder Formamid ist.

5. Verfahren zur Herstellung von S-Nicotin nach Anspruch 1, **dadurch gekennzeichnet, dass** bei S1 ein molares Verhältnis des Nicotinats zum γ-Butyrolacton zum Basenkatalysator 1:(1-2):(1,2-3) beträgt.

6. Verfahren zur Herstellung von S-Nikotin nach Anspruch 1, **dadurch gekennzeichnet, dass** bei S5 die Base Hydroxid oder Carbonat ist.

Revendications

1. Procédé de préparation de S-nicotine, **caractérisé par** le fait de comprendre les étapes suivantes :

S1 : ajouter du nicotinate et de la γ-butyrolactone dans un solvant organique I, réaliser une condensation en présence d'un catalyseur de base pour obtenir un produit de condensation, et réaliser une cyclisation sur le produit de condensation en présence d'acide chlorhydrique pour obtenir de la 4-chloro-1-(3-pyridine)-1-butanone ;
S2 : faire réagir la 4-chloro-1-(3-pyridine)-1-butanone avec un réactif d'amination dans des conditions alcalines pour obtenir de la 4-amino-1-(3-pyridine)-1-butanone ;
S3 : ajouter la 4-amino-1-(3-pyridine)-1-butanone et du chloroborane de (+)-B-diisopinocamphéyle dans un solvant organique II, et faire réagir à -30 à 10 °C pour obtenir du (S)-4-amino-1-(pyridin-3-yl)butan-1-ol ;
S4 : faire réagir le (S)-4-amino-1-(pyridin-3-yl)butan-1-ol avec un réactif de chloration pour obtenir du (S)-4-amino-1-(pyridin-3-yl)butyle-1-chlore ;
S5 : réaliser une cyclisation sur le (S)-4-amino-1-(pyridin-3-yl)butyle-1-chlore en présence d'une base pour obtenir de la S-déméthylnicotine ; et

S6 : faire réagir la S-déméthylnicotine avec un réactif de méthylation d'amine pour obtenir de la S-nicotine brute, et purifier pour obtenir de la S-nicotine ;
dans lequel à S1, le catalyseur de base est sélectionné parmi un ou plusieurs éléments parmi un alcoxyde de métal alcalin, un hydrure de métal alcalino-terreux, un oxyde de métal alcalino-terreux, une amine, un sel métallique d'amine, un hydroxyde, un carbonate et un bicarbonate ;
à S3, le solvant organique II est sélectionné parmi un ou plusieurs éléments parmi le tétrahydrofurane, le diméthyltétrahydrofurane et le 1,4-dioxane ;
à S4, le réactif de chloration est le chlorure d'oxalyle ; et un rapport molaire du (S)-4-amino-1-(pyridin-3-yl)butan-1-ol sur le chlorure d'oxalyle est de 1:(1 à 3) ; et
à S2, un rapport molaire de la 4-chloro-1-(3-pyridine)-1-butanone sur le réactif d'amination est de 1 :(1 à 3).

2. Procédé de préparation de S-nicotine selon la revendication 1, **caractérisé en ce qu'**à S3, un rapport molaire de la 4-amino-1-(3-pyridine)-1-butanone sur le chloroborane de (+)-B-diisopinocamphéyle est de 1:(1 à 3).

3. Procédé de préparation de S-nicotine selon la revendication 4, **caractérisé en ce qu'**à S4, la température de réaction est de -10 à 10 °C.

4. Procédé de préparation de S-nicotine selon la revendication 1, **caractérisé en ce qu'**à S2, le réactif d'amination est l'hydroxyde d'ammonium ou le formamide.

5. Procédé de préparation de S-nicotine selon la revendication 1, **caractérisé en ce qu'**à S1, un rapport molaire du nicotinate sur la γ-butyrolactone sur le catalyseur de base est de 1:(1 à 2):(1,2 à 3).

6. Procédé de préparation de S-nicotine selon la revendication 1, **caractérisé en ce qu'**à S5, la base est un hydroxyde ou carbonate.

REFERENCES CITED IN THE DESCRIPTION

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